Diagnosis and management of resistant hypertension

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ABSTRACT

Resistant hypertension is defined as blood pressure that remains above the therapeutic goal despite concurrent use of at least three antihypertensive agents of different classes, including a diuretic, with all agents administered at maximum or maximally tolerated doses. Resistant hypertension is also diagnosed if blood pressure control requires four or more antihypertensive drugs. Assessment requires the exclusion of apparent treatment resistant hypertension, which is most often the result of non-adherence to treatment. Resistant hypertension is associated with major cardiovascular events in the short and long term, including heart failure, ischemic heart disease, stroke, and renal failure. Guidelines from several professional organizations recommend lifestyle modification and antihypertensive drugs. Medications typically include an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, a calcium channel blocker, and a long acting thiazide-type/like diuretic; if a fourth drug is needed, evidence supports addition of a mineralocorticoid receptor antagonist. After a long pause since 2007 when the last antihypertensive class was approved, several novel agents are now under active development. Some of these may provide potent blood pressure lowering in broad groups of patients, such as aldosterone synthase inhibitors and dual endothelin receptor antagonists, whereas others may provide benefit by allowing treatment of resistant hypertension in special populations, such as non-steroidal mineralocorticoid receptor antagonists in patients with chronic kidney disease. Several device based approaches have been tested, with renal denervation being the best supported and only approved interventional device treatment for resistant hypertension.

Introduction

Hypertension, or high blood pressure, is the world's leading risk factor for morbidity and mortality,[1] and resistant hypertension represents an extreme facet of the syndrome. Patients with resistant hypertension have uncontrolled blood pressure despite treatment with optimal or maximally tolerated doses of three different antihypertensive drug classes, including a diuretic.[2 3] Resistant hypertension is also diagnosed if blood pressure control requires four or more antihypertensive drugs. Diagnosis of resistant hypertension requires exclusion of apparent treatment resistant hypertension, the main causes of which are medication non-adherence, white coat effect, and improper blood pressure measurement technique (fig 1).

Blood pressure is continuously related to risk of fatal stroke, ischemic heart disease, and non-cardiac vascular disease throughout the normal range down to 115/75 mm Hg, and each increase of 20 mm Hg systolic pressure or 10 mm Hg diastolic pressure above this doubles the risk of a fatal cardiovascular event.[4] Patients with resistant hypertension have the highest risk of cardiovascular complications. The five year retrospective cohort Kaiser Permanente Study compared 60 327 patients with resistant hypertension and 410 059 patients with non-resistant hypertension.[5] Patients with resistant hypertension had a 46% higher risk of heart failure, a 32% higher risk of end stage renal disease, a 24% higher risk of an ischemic cardiac event, and a 6% higher risk of death. In another retrospective study of more than 200 000 patients with incident hypertension, those with resistant hypertension were 47% more likely to have combined outcomes of death, myocardial infarction, heart failure, stroke, or chronic kidney disease (CKD) over the median 3.8 years of follow-up.[6] Patients with CKD have a much higher prevalence of resistant hypertension than does the general hypertensive population, and those with resistant hypertension also have a markedly higher incidence of cardiovascular disease and end stage renal disease than those without resistant hypertension.[7] A high prevalence of resistant hypertension also occurs in Black patients and in patients with diabetes.[8]

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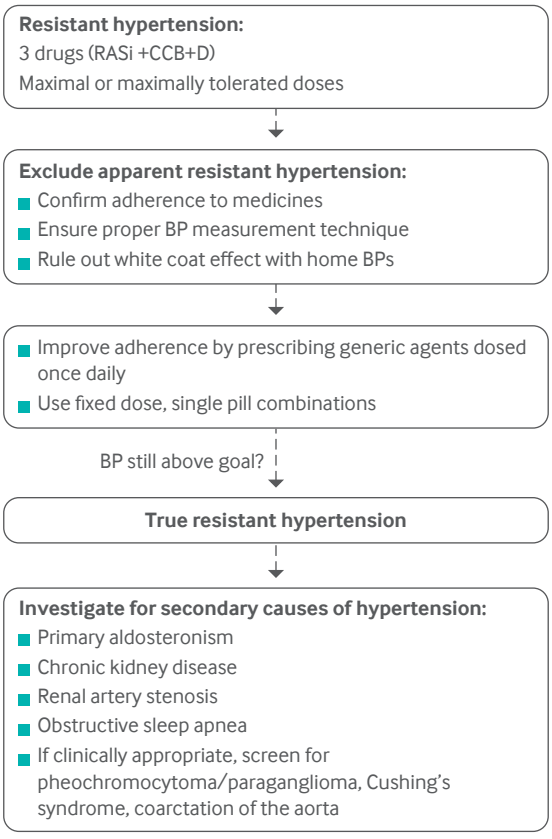
Resistant hypertension:
3 drugs (RASi +CCB+D)
Maximal or maximally tolerated doses
Exclude apparent resistant hypertension:
Confirm adherence to medicines
Ensure proper BP measurement technique
Rule out white coat effect with home BPs
Improve adherence by prescribing generic agents dosed once daily
Use fixed dose, single pill combinations
BP still above goal?
True resistant hypertension
Investigate for secondary causes of hypertension:
Primary aldosteronism
Chronic kidney disease
Renal artery stenosis
Obstructive sleep apnea
If clinically appropriate, screen for pheochromocytoma/paraganglioma, Cushing's syndrome, coarctation of the aorta

Fig 1 | Diagnosis and evaluation of resistant hypertension. BP=blood pressure; CCB=calcium channel blocker; D=diuretic; RASi=renin-angiotensin system inhibitor

This review aims to present an overview of resistant hypertension, including a review of its diagnosis, evaluation, and management. We summarize the latest treatments for resistant hypertension, including new and emerging drugs as well as devices. The review is aimed at both general practitioners who provide primary care for patients with this frequent presentation of high blood pressure and specialists (typically nephrologists, cardiologists, and endocrinologists) to whom many of these patients are referred for investigation and management.

Sources and selection criteria

We searched PubMed by using the following terms: "resistant hypertension", "true resistant hypertension", "adherence to treatment", "management of resistant hypertension", "renal denervation", and "devices for treatment of resistant hypertension". Search dates were between 1 January 2010 and 19 February 2024. We selected papers published in English in peer reviewed scientific journals of impact factor >3 in the past five years. We included guidelines and systematic reviews with meta-analysis and randomized controlled trials (RCTs), as well as observational studies detailing the epidemiology and pathophysiology of resistant hypertension. We also included animal and human pathophysiology studies from the 1990s to the present. We excluded case reports.

Epidemiology

An accurate determination of the prevalence of resistant hypertension is difficult to obtain because the diagnosis is often made incorrectly. Reported prevalence has varied by population studied, ranging from 12% to 18% of all patients with hypertension in a meta-analysis of 24 studies and reported in a scientific statement prepared by the American Heart Association (AHA).[2 9] Importantly, almost all published reports likely overestimated the prevalence of the condition. Most studies on prevalence did not incorporate the critical elements to exclude apparent treatment resistant hypertension: out-of-office blood pressure measurements to exclude white coat hypertension, rigorous methods for measuring blood pressure,[10] and systematic testing for adherence to medication. A systematic review and meta-analysis of 91 studies parsed these details and found a 10% prevalence of true resistant hypertension, reaching 22.9% in patients with CKD.[11]

A more extreme phenotype has been described and labeled refractory hypertension.[12] Medical treatment for hypertension in these patients typically fails despite the use of five or more agents; this variant is rare.[13] The initial single center retrospective analysis defined these patients by blood pressure remaining uncontrolled after at least three visits to a specialty clinic and showed both higher blood pressure and higher heart rate, suggesting persistent activation of the sympathetic nervous system as causal.[12] Examination of a large population based cohort found no difference in heart rate between patients defined as having refractory hypertension and those with resistant hypertension.[13] Importantly, rigorous testing for adherence to medication was not done in either study.

Diagnosis and evaluation

Evaluation of resistant hypertension begins with accurate blood pressure measurements, as improper techniques (for example, improper cuff size, incorrect arm positioning) can result in falsely high readings (fig 1). Exclusion of the white coat effect with ambulatory blood pressure or home blood pressure monitoring done according to guidelines is also important.[14] Automated office blood pressure (AOBP) measurement done with a specialized oscillometric device allows for repeated blood pressure measures, one to two minutes apart, with the patient seated alone in a quiet room (unattended). In a meta-analysis of comparative studies, AOBP measurements did not differ significantly from home blood pressure measurements,[15] thus offering value in reducing the white coat effect. AOBP is the recommended method of office measurement in Hypertension Canada guidelines.[16 17] Finally, the diagnosis of true resistant hypertension can be made only if patients are taking their medications as prescribed.

Assessing non-adherence

Non-adherence accounts for 25-50% of apparent treatment resistant hypertension.[18] Polypharmacy

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is an important contributor. In a multicenter study testing urine and serum in 1348 patients, the rates of non-adherence increased with each increase in the number of medications.[19] Twenty four studies measuring adherence among patients with uncontrolled hypertension despite at least three antihypertensive drugs of different classes being prescribed were included in a meta-analysis that showed a pooled prevalence of non-adherence of 31.2% (95% confidence interval 20.0% to 44.7%).[20] The highest pooled estimates of non-adherence were for therapeutic drug monitoring and directly observed therapy (47.9%); the lowest were for indirect methods, such as self-reporting (3.3%). Studies of non-adherence using objective measures of drugs or metabolites in blood or urine have consistently shown a very high rate of non-adherence (around 50%) in patients with resistant hypertension.[21-24] This number is similar to adherence rates in a large series of patients in clinical trials with electronic monitoring of medications.[25] On the other hand, the prevalence of true resistant hypertension is likely in single digits when patients with non-adherence are excluded.[26] Evidence supporting protocols to improve adherence in patients with resistant hypertension is sparse, but practices shown to be successful in general populations of patients with hypertension are advised (table 1): prescribe agents that are dosed once daily; use fixed dose, single pill combinations when possible; use low cost and generic agents; and consolidate refills (fig 1).[27 28]

Screening for secondary causes of hypertension

All patients with resistant hypertension warrant an evaluation for secondary causes (fig 1). A common and often overlooked cause is primary aldosteronism, with a prevalence of at least 10% among all hypertensive patients and 25% in those with resistant hypertension.[29 30] Renal vascular hypertension is a rarer cause that can result from either fibromuscular dysplasia (usually but not always in younger people[31]) or atherosclerotic vascular disease. Atherosclerotic vascular disease and CKD are increasingly important contributors to resistant hypertension with advancing age. Rare causes of resistant hypertension include coarctation of the aorta and the endocrine diseases of pheochromocytoma, Cushing's syndrome, apparent mineralocorticoid excess/11β-hydroxylase deficiency, hyperdeoxycorticosteronism (congenital adrenal hyperplasia, primary cortisol resistance, deoxycorticosterone producing tumor), hypothyroidism or hyperthyroidism, primary hyperparathyroidism, and acromegaly.[2]

Primary aldosteronism

Primary aldosteronism is a group of disorders marked by inappropriate, non-suppressible aldosterone production independent of renin, suppressed baseline renin secretion, and inability to stimulate renin secretion normally.[30] Hypertension in primary aldosteronism is primarily due to extracellular fluid volume expansion, resulting in decreased renin. Several histopathologic changes have been identified in adrenal glands of patients with primary aldosteronism, on the basis of expression of CYP11B2 (aldosterone synthase). A recent international consensus for nomenclature endorsed by the World Health Organization proposed the following correlates for primary aldosteronism: diffuse adrenal cortical hyperplasia, adrenal cortical nodular disease, adrenal cortical adenomas, and the rare adrenal cortical carcinomas.[32] Multiple adenomas can co-occur in one or both adrenal glands. Genetics underlying unusual familial forms of hyperaldosteronism are recognized, including glucocorticoid remediable aldosteronism (familial hyperaldosteronism type 1) (~1%), due to a chimeric *CYP11B1/CYP11B2* gene,[33] and familial hyperaldosteronism type II, the most common form of familial hyperaldosteronism (~6%), due to *CLCN2* chloride channel mutations.[34] Familial hyperaldosteronism type III is very rare (caused by germline mutations in *KCNJ5*), often associated with massive adrenal gland enlargement and severe hypertension from childhood that may require early bilateral adrenalectomy.[35] Familial hyperaldosteronism type IV (germline *CACNA1H* variants) is also rare.[36]

The importance of diagnosing and treating primary aldosteronism derives in part from the pro-inflammatory and pro-fibrotic effects, as well as endothelial dysfunction associated with aldosterone.[37] Primary aldosteronism leads to a striking increase in the relative risk of atrial fibrillation, stroke, myocardial infarction, increased left ventricular hypertrophy, and diastolic dysfunction, stiffening of large arteries, widespread tissue fibrosis, and remodeling of resistance vessels.[38-40] A systematic meta-analysis comparing 3838 patients with primary aldosteronism and 9284

Table 1 | Drug classes to treat resistant hypertension

Class	Notes
First three medications: angiotensin receptor blocker/ACE inhibitor, calcium channel blocker, diuretic	Choose long acting drugs, once daily dosing
	Substitute thiazide-like diuretic, chlorthalidone, or indapamide
Fourth line: add mineralocorticoid receptor antagonist (spironolactone or eplerenone)	Spironolactone once daily, more potent; eplerenone in males, dosed twice daily
Additional approved classes to consider: β blockers, central α agonist (clonidine)	Follow heart rate; consider combined α-β blockade; weekly patch aids adherence
Hydralazine	Best for temporary blood pressure control
Minoxidil	Side effects often limiting, including volume retention and tachycardia

ACE=angiotensin converting enzyme.

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patients with primary hypertension reported that patients with primary aldosteronism had a 2.58-fold higher risk of stroke, 1.77-fold higher risk of coronary artery disease, 3.52-fold higher risk of atrial fibrillation, and twice as much heart failure at 8.8 years from the diagnosis of hypertension.[40] Primary aldosteronism also increases the risk of diabetes, metabolic syndrome, and left ventricular hypertrophy.[40 41] Accordingly, primary aldosteronism through prolonged exposure to excess aldosterone results in increased risk of cerebral-cardiovascular events and target organ damage.[42]

Who should be screened for primary aldosteronism?

The classic presentation of primary aldosteronism was hypertension with hypokalemia and an adrenal adenoma, but normokalemic hypertension is now its most common presentation, with hypokalemia present only in the more severe cases.[43] Therefore, recommendations have expanded beyond the original criteria, which included true resistant hypertension, spontaneous or diuretic induced hypokalemia, and adrenal adenoma. The British and Irish Hypertension Society guidelines recommend that all adults with hypertension under the age of 40 should also be screened.[44] Expert US guidance advises screening also in patients with severe hypertension, hypertension with obstructive sleep apnea, family history of early onset hypertension or cerebrovascular accident before 40 years of age, and hypertension with atrial fibrillation, as well as all hypertensive first degree relatives of patients with primary aldosteronism.[30 45 46] Many experts consider screening all patients with stage 2 hypertension for primary aldosteronism to be valuable. Screening involves the simultaneous measurement of aldosterone and renin (activity or mass). The aldosterone/renin ratio is falling out of favor; a suppressed renin with inappropriate aldosterone secretion represents a positive screen.[41 47] Screening rates are dismally low, in low single digits even among patients with high prevalence of primary aldosteronism such as those with resistant hypertension and those with classic hypertension plus hypokalemia.[48 49] Especially given the high prevalence of the disease and evidence that it carries increased risk of cardiovascular disease, screening, confirmation, imaging, and diagnostic recommendations are rapidly changing, and guidelines are in the midst of necessary updates.[44 46 50]

How should primary aldosteronism be treated?

Surgical removal is considered the best treatment for unilateral adenoma after lateralization of aldosterone secretion has been confirmed, which is often challenging and best carried out in specialized centers with experience in adrenal vein sampling. Antihypertensive medication is indicated for bilateral disease and for patients who are not surgical candidates. Medical treatment requires increasing doses of spironolactone or eplerenone until renin becomes unsuppressed. Eplerenone is often prescribed for men to avoid the anti-androgenic effects of spironolactone; it generally must be administered twice daily to obtain an adequate blood pressure response. Thiazide diuretics and/or calcium channel blockers (CCBs) may be needed to achieve goal blood pressure. Future medical therapy for primary aldosteronism may look very different with the advent of aldosterone synthase inhibitors (ASIs), as described below.

Renal vascular hypertension

Renal vascular hypertension is another important contributor to resistant hypertension, with most cases being caused by atherosclerotic disease. Fibromuscular dysplasia is a less common but often curable cause, found more often but not only in younger patients. Evaluation and treatment of this condition have shifted greatly after several prospective randomized trials failed to show that renal vascularization is more effective than medical treatment for most patients with atherosclerotic renovascular hypertension.[51 52] Guidance from the AHA reinforces that optimizing medical therapy is generally considered primary treatment.[53] Following intensive control of blood pressure and lipids and smoking cessation, clinical judgment is needed to assess whether the clinical scenario suggests a potential benefit of imaging and intervention with stenting or balloon angioplasty. Imaging approaches include renal artery duplex ultrasonography, often as first line, or computed tomographic or magnetic resonance angiography.[53] Observational data and a post hoc analysis of the CORAL trial have shown that blood pressure can be controlled and mortality improved after revascularization in some patients.[54 55] Percutaneous revascularization is advised by the American College of Cardiology/AHA guideline for hemodynamically significant renal artery stenosis in most patients with fibromuscular dysplasia of a renal artery or any one of the following conditions in atherosclerotic renovascular hypertension: accelerated, resistant, or malignant hypertension unresponsive to full dose antihypertensive treatment; progressive deterioration in renal function; recurrent congestive heart failure or sudden unexplained "flash" pulmonary edema; and unstable angina.[56]

Management of resistant hypertension

The risk of cardiovascular disease can be reduced with effective antihypertensive therapy.[57] Control of blood pressure results in greater reduction of mortality in populations than does treatment of other chronic conditions.[58] Risk is reduced at the population level with as little as a 2 mm Hg reduction in blood pressure, and continuous reduction in cardiovascular disease is seen as lower levels of systolic blood pressure are achieved. A 10 mm Hg lower systolic or 5 mm Hg lower diastolic blood pressure predicts a 40% reduction in risk of stroke and a 30% reduction in risk of ischemic heart disease, and a 5 mm Hg reduction in systolic blood

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pressure decreased the risk of major cardiovascular events by 10%.[59 60] Similar reductions have been detected for stroke, coronary heart disease, and all cause mortality.[61] Specifically applied to patients with resistant hypertension, as shown by a secondary analysis of SPRINT, intensive blood pressure lowering is superior to standard treatment in terms of cardiovascular disease outcomes irrespective of the drugs used.[62]

Identify and reverse contributing lifestyle factors

Lifestyle factors contributing to true resistant hypertension include obesity, high dietary sodium intake, alcohol intake, physical inactivity, and poor dietary pattern (fig 2). A recent meta-analysis found that weight loss diets lower blood pressure among patients with hypertension by 4.5/3.2 mm Hg compared with controls.[63] Salt restriction is critical, as recommended in AHA guidelines for a daily sodium intake of <1500 mg/day and demonstrated in two studies showing efficacy in small numbers of patients with resistant hypertension.[64 65] Reduction of alcohol intake is recommended for patients with resistant hypertension, as in all patients with hypertension.[14 66 67]

In the TRIUMPH (Treating Resistant Hypertension Using Lifestyle Modification to Promote Health) RCT,[68] 140 patients with resistant hypertension (including 31% with diabetes and 21% with CKD) were randomized to a four month program of lifestyle modification including dietary counseling, behavioral weight management, and exercise or a single counseling session providing standardized education. The structured diet and exercise program was associated with a greater reduction in clinic systolic blood pressure compared with physician's advice (−12.5 (95% confidence interval −14.9 to −10.2) mm Hg versus −7.1 (−10.4 to −3.7) mm Hg; P=0.005), as well as a significant fall in ambulatory systolic blood pressure (−7.0 (−8.5 to −4.0) mm Hg versus −0.3 (−4.0 to 3.4) mm Hg; P=0.001).

Discontinue or minimize interfering substances

Drugs can contribute to true resistant hypertension by direct pressor action or by interfering with the action of antihypertensive drugs. Common examples are non-steroidal anti-inflammatory drugs through inhibition of vasodilator prostacyclin synthesis, combined oral contraceptives and hormone replacement therapy through enhanced angiotensinogen in the circulation, cocaine and amphetamines, sympathomimetic amines in decongestants and antitussives via their vasoconstrictor effects, and antidepressants (table 2).[69] Other agents that can raise blood pressure include immunosuppressive drugs, tyrosine kinase inhibitors such as sunitinib used in oncologic therapy that may act by inducing vascular rarefaction, and recombinant erythropoietin, which may exert its effects on blood pressure in part through enhanced activity of the endothelin system.[70]

Drug treatment of resistant hypertension

Non-adherence should always be investigated thoroughly and intensive directed efforts made to optimize patients' ability to take their prescribed medications. Multiple management strategies to improve adherence include prescribing generic, once daily medications covered by the patient's insurance plan and fixed dose, single pill combination dosing when possible (fig 1). Education strategies and tracking and medication reminders are complementary.[71] Adherence related to single versus multiple pills has been shown to result in improved cardiovascular outcomes,[72] and improved

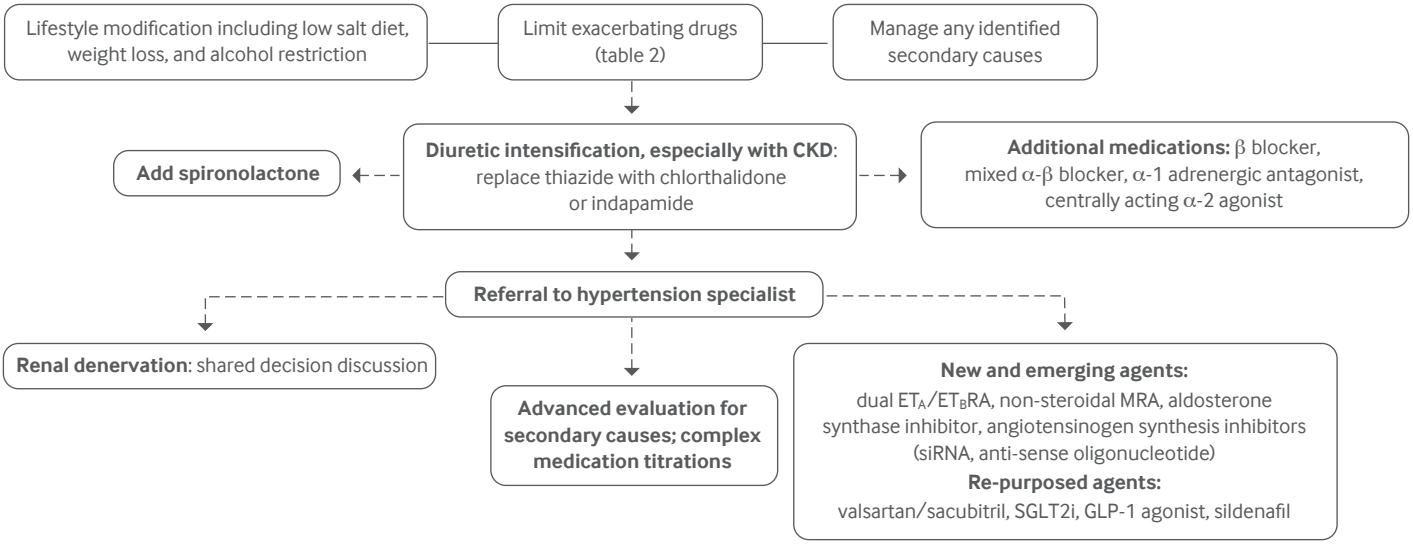
Lifestyle modification including low salt diet, weight loss, and alcohol restriction
Limit exacerbating drugs (table 2)
Manage any identified secondary causes
Add spironolactone
Diuretic intensification, especially with CKD: replace thiazide with chlorthalidone or indapamide
Additional medications: β blocker, mixed α-β blocker, α-1 adrenergic antagonist, centrally acting α-2 agonist
Referral to hypertension specialist
Renal denervation: shared decision discussion
Advanced evaluation for secondary causes; complex medication titrations
New and emerging agents: dual ETA/ETBRA, non-steroidal MRA, aldosterone synthase inhibitor, angiotensinogen synthesis inhibitors (siRNA, anti-sense oligonucleotide)
Re-purposed agents: valsartan/sacubitril, SGLT2i, GLP-1 agonist, sildenafil

Fig 2 | Management of resistant hypertension, including intensification of treatment and referral for management. CCB=calcium channel blocker; D=diuretic; ET_A=endothelin type A receptor; ET_B=endothelin type B receptor; MRA=mineralocorticoid receptor antagonist; RASi=renin-angiotensin system inhibitor; SGLT2i=sodium-glucose cotransporter type 2 inhibitor

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Table 2 | Interfering substances that raise blood pressure

Substance	Mechanism
Non-steroidal anti-inflammatory drugs	Inhibition of vasodilator prostacyclin synthesis
Combined oral contraceptives and hormone replacement therapy	Increased angiotensinogen production; RAS activation
Recreational drugs: cocaine, amphetamines and derivatives	Vasoconstriction and tachycardia
Anorectic agents: phentermine	Vasoconstriction and tachycardia
ADHD stimulants: methylphenidate	Vasoconstriction and tachycardia
Sympathomimetic amines in decongestants and antitussives: pseudoephedrine, phenylephrine	Vasoconstriction
Antidepressants: MAO inhibitors, tricyclic antidepressants, SNRIs, bupropion	Adrenergic activation; some have effects on serotoninergic, cholinergic, and histaminergic pathways; some can cause orthostatic hypotension
Biologic therapies: tyrosine kinase inhibitors (eg, sunitinib, sorafenib)	Vascular rarefaction
VEGF inhibitors: bevacizumab	Vascular rarefaction
Immunosuppressive drugs: cyclosporine, tacrolimus	Enhanced activity of endothelin system with cyclosporine and tacrolimus, and also reduced anti-inflammatory T regulatory lymphocytes with tacrolimus, inducing a pro-inflammatory phenotype
Recombinant erythropoietin	Enhanced activity of endothelin system
Exogenous steroids: glucocorticoids, mineralocorticoids	Volume expansion, increased cardiac output and vascular tone
Herbs/supplements: ginseng, natural licorice, yohimbine	Licorice through inhibition of 11β-hydroxysteroid dehydrogenase type 2 resulting in apparent mineralocorticoid excess
	Yohimbine via α2 adrenergic receptor antagonism and increased sympathetic activity

ADHD=attention deficit/hyperactivity disorder; MAO=monoamine oxidase; RAS=renin-angiotensin system; SNRI=serotonin-norepinephrine reuptake inhibitor; VEGF=vascular endothelial growth factor.

persistence with single pill combinations was associated with reduced all cause mortality in the START study.[73]

The recommended first three drugs for the treatment of resistant hypertension are an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), a calcium channel antagonist, and a long acting thiazide or thiazide-like diuretic. Guidelines have recommended chlorthalidone and indapamide because of greater efficacy than hydrochlorothiazide,[74-76] although hydrochlorothiazide is prescribed more widely. A large pragmatic trial that randomized more than 13 000 patients in the Department of Veterans Affairs health system failed to show a lower occurrence of major cardiovascular outcomes in patients taking chlorthalidone compared with those taking hydrochlorothiazide.[77] Similar negative results were seen in a cohort study of 12 700 adults and in the LEGEND observational comparative cohort study of more than 730 000 people.[78 79] In the US, hydrochlorothiazide is widely available in combination with multiple ACE inhibitors and ARBs, but chlorthalidone is not. The decision to change hydrochlorothiazide to chlorthalidone must be weighed against the potential burden of adding an extra pill.

If blood pressure remains above goal, evidence supports adding the mineralocorticoid receptor antagonist (MRA) spironolactone as the fourth drug. The PATHWAY-2 RCT was a double blind, placebo controlled, crossover trial that compared spironolactone with placebo, doxazosin, or bisoprolol as the fourth drug in 285 patients with resistant hypertension already treated with an ACE inhibitor/ARB, a CCB, and a diuretic.[80] Reduction in home measured systolic blood pressure was greater with spironolactone (12.8 mm Hg) than with placebo (−8.70 (95% confidence interval −9.72 to −7.69) mm Hg; P<0.001), doxazosin (−4.03 (−5.04 to −3.02) mm Hg; P<0.001), or bisoprolol (−4.48 (−5.50 to −3.46) mm Hg; P<0.001). As spironolactone has anti-androgenic actions, the more selective but less potent MRA eplerenone is often preferred in male patients, as it is associated with lower rates of impotence and gynecomastia. Patients with advanced CKD were excluded from the PATHWAY-2 study. In patients with reduced renal function, the risk of hyperkalemia may favor the use of non-steroidal MRAs (nsMRAs), although they are weaker antihypertensives. Alternately, the AMBER trial showed that the potassium binding agent patiromer can allow use of spironolactone in patients with resistant hypertension and impaired renal function.[81] The AMBER trial included 295 patients randomly assigned to spironolactone in addition to double blind treatment with either placebo (n=148) or patiromer (n=147). After 12 weeks, 98 of 148 patients in the placebo group and 126 of 147 patients in the patiromer group remained on spironolactone (between group difference 19.5%, 95% confidence interval 10.0 to 29.0; P<0.001). Adverse events in 79 of 148 patients in the placebo group and 82 of 147 patients in the patiromer group were mild or moderate in severity. Whereas US guidelines advise spironolactone as fourth line agent, the 2023 European Society of Hypertension (ESH) guidelines recommend that the fourth drug should be chosen on the basis of estimated glomerular filtration rate (eGFR): spironolactone in patients with eGFR >30 mL/min and chlorthalidone in those with eGFR <30 mL/min.[67] Overall adoption of recommendations has been poor in the management of patients presenting with resistant hypertension.[2] Only 3.2% of US adults (NHANES 2009-14) with apparent resistant hypertension were taking chlorthalidone or indapamide, and only 9% were taking spironolactone or eplerenone.[18]

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If blood pressure remains uncontrolled despite the use of four drugs, an agent from an additional class may be added, including a β blocker, α blocker, α agonist such as clonidine, vasodilator such as hydralazine (combined with a β blocker), or minoxidil, the last of these particularly in patients with CKD (also combined with a β blocker and a loop diuretic or chlorthalidone as shown to be effective in patients with CKD[82]). The ESH/European Society of Cardiology (ESC) guidelines no longer recommend minoxidil owing to its side effects of heart rate elevation and fluid retention.[67] The addition of β blockade counters the tachycardic response to vasodilators that could trigger myocardial ischemia in these patients. However, no trial data guide management at this point, and referral of these patients to a hypertension specialist is recommended. Figure 2 depicts the intensification of treatment and referral for management of resistant hypertension.

Newer treatments for resistant hypertension

In recent years, new drugs have been developed that may have a role in the treatment of resistant hypertension (table 3). These include endothelin antagonists, aldosterone synthase inhibitors, novel nsMRAs, and inhibitors of angiotensinogen production by the liver with small interfering RNA (siRNA), as well as atrial natriuretic peptides and aminopeptidase A inhibitors.

Endothelin receptor antagonists

Endothelin antagonists are approved for the treatment of primary pulmonary hypertension, but theoretical reasoning suggests that agents blocking this system would be effective in systemic hypertension. Endothelin is a powerful vasoconstrictor 21 amino acid peptide present in many tissues.[83 84] The endothelin system is activated in the vasculature of patients with difficult-to-control hypertension,[85] suggesting value for its blockade in resistant hypertension. Figure 3 depicts the vascular endothelin system and the effect of endothelin receptor antagonists.

The dual ET_A receptor/ET_B receptor antagonist bosentan reduced blood pressure in a clinical trial of 293 patients with hypertension.[86] This drug was abandoned for primary hypertension because of adverse effects (elevations in liver enzymes). The ET_A receptor selective antagonist darusentan did not significantly lower office measured blood pressure in a small study,[87] despite a significant reduction in ambulatory blood pressure,[88] and clinical development was abandoned. With the arrival of aprocitentan, a second dual ET_A receptor/ET_B receptor antagonist with few adverse side effects and a positive phase II trial showing significant blood pressure reduction in hypertensive volunteers, endothelin antagonism became a potential contender for the treatment of hypertension.[89]

The PRECISION trial in resistant hypertension assessed the ability of aprocitentan to reduce blood pressure in 730 patients with resistant hypertension, all taking maximally tolerated doses of three first line antihypertensive agents including a diuretic.[90] This multicenter, randomized, parallel group, phase III study included a double blind, placebo controlled four week segment during which all patients placed on the same fixed dose triple combination pill were randomized to aprocitentan or placebo. A single (patient) blind period followed during which everyone was treated with 25 mg aprocitentan to test for efficacy and sustained response at 40 weeks. Automated office measured systolic blood pressure, the primary endpoint at four weeks, was reduced significantly by a mean 15.3 mm Hg with aprocitentan12.5 mg, 15.2 mm Hg with 25 mg, and 11.5 mm Hg with placebo, resulting in a difference versus placebo of −3.8 (standard deviation 1.3; 97.5% CI −6.8 to −0.8) mm Hg; P=0.004) and −3.7 (1.3; −6.7 to −0.8) mm Hg; P=0.005), respectively. Twenty four hour ambulatory systolic blood pressure showed similar reductions relative to placebo. A 12 week, double blind, randomized, placebo controlled withdrawal segment was included, in which patients were re-randomized to continue aprocitentan 25 mg or change to placebo. After four weeks of aprocitentan withdrawal, office systolic blood pressure was significantly higher in patients taking placebo compared with aprocitentan (5.8 (95% CI 3.7 to 7.9) mm Hg; P<0.001). The most frequent side effect was mild-to-moderate edema in 9% of patients at 12.5 mg and 18% at 25 mg. The adverse side effect of edema may limit use of these agents. Combining this drug with a diuretic may be optimal to counteract fluid retention.

Table 3 | Novel/emerging drug classes

Drugs	Notes
Dual ET_A/ET_B receptor antagonist	Aprocitentan approved by FDA March 2024 in combination with other antihypertensives; volume retention may limit use
Aldosterone synthase inhibitors	For RH and perhaps especially for primary aldosteronism: baxdrostat, lorundrostat, dexfadrostat in development
Non-steroidal MRA	Finerenone approved in US and Canada for diabetic kidney disease; esaxerenone approved in Japan for primary hypertension; ocedurenone, aparenone under investigation especially for hypertension in patients with CKD/diabetic kidney disease
Angiotensinogen synthesis inhibitors	Zilebesiran, IONIS-AGT-LRx under investigation
ARB + neprilysin inhibitor	Entresto approved in some countries for hypertension + heart failure
M-atrial natriuretic peptide	To date, only one small open label, single dose small trial showing lowering of BP with increase in urinary sodium excretion
Firibastat	Aminopeptidase A inhibitor lowered BP in multicenter, open label, phase IIb study, but failed against placebo in FRESH study in RH

AGT=angiotensinogen; ARB=angiotensin receptor blocker; BP=blood pressure; CKD=chronic kidney disease; ET=endothelin; FDA=Food and Drug Administration; MRA=mineralocorticoid antagonist; RH=resistant hypertension.

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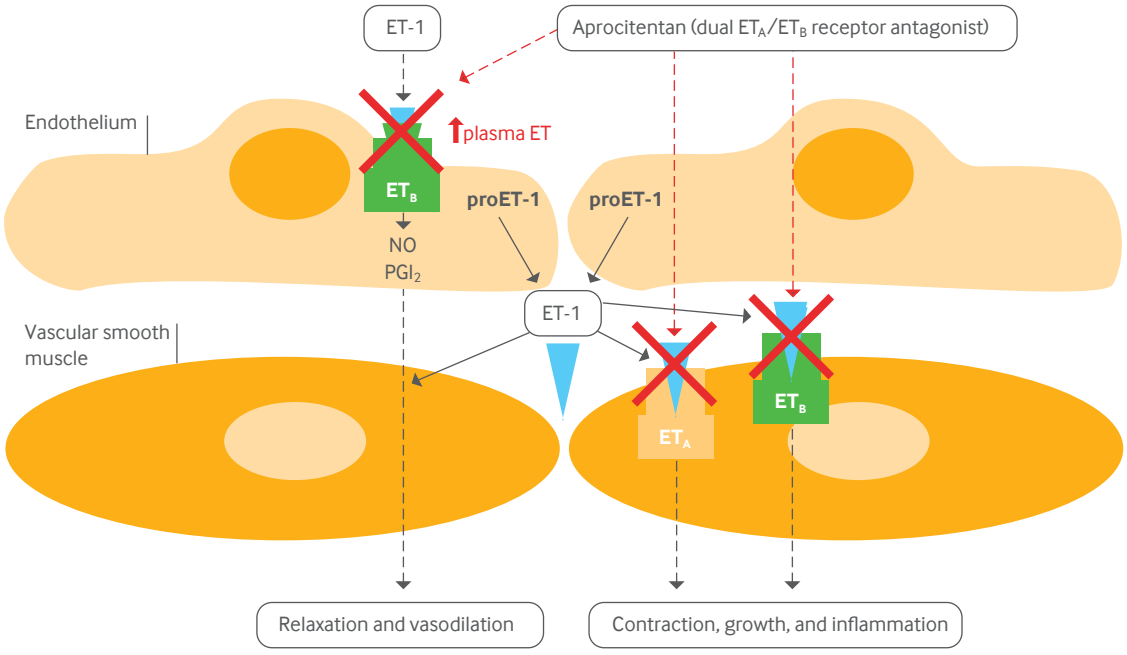

Fig 3 | The vascular endothelin (ET) system. ET-1 formed from proET-1 is released by endothelium and acts on smooth muscle cell ET_A and ET_B receptors to induce contraction, growth, and inflammation. In an autocrine fashion, it acts on ET_B endothelial receptors to stimulate generation of nitric oxide (NO) and prostacyclin (PGI_2). Aprocitentan, the ET_A/ET_B dual endothelin receptor antagonist, lowers blood pressure by blocking vasoconstriction, stiffening of vessels, and inflammation mediated by smooth muscle ET_A and ET_B receptors. Blockade of endothelial ET_B receptors reduces clearance function of these and results in increased plasma concentration of ET-1

Other drugs in the endothelin receptor antagonist group are under development, but to date aprocitentan stands alone with proven safety and efficacy in resistant hypertension. In contrast to MRAs, aprocitentan does not induce hyperkalemia, thereby allowing use in patients with advanced CKD. In PRECISION, patients with CKD showed a greater response to the drug. In addition, its long half life of 44 hours provides benefit in maintaining blood pressure lowering throughout the 24 hour day. However, given its modest efficacy, risk of edema, and potential cost, this agent may be best reserved for patients with hyperkalemia, CKD, or both. Aprocitentan has been approved by the US Food and Drug Administration (FDA) for use in combination with other antihypertensive agents in adults with treatment resistant hypertension.

Novel non-steroidal mineralocorticoid antagonists

Despite the proven efficacy of spironolactone in resistant hypertension, which justifies its choice as the fourth agent for resistant hypertension in US guidelines,[14] its anti-androgenic effects and potential for hyperkalemia in the setting of compromised renal function are drawbacks. Although eplerenone is a selective MRA, it is a weaker antihypertensive and can also induce hyperkalemia in patients with CKD. Non-steroidal MRAs are members of a new class of selective agents with high affinity and specificity for the mineralocorticoid receptor.[91] nsMRAs act as bulky inverse agonists, inhibiting co-regulator recruitment even in the absence of aldosterone, whereas the steroidal MRAs spironolactone and eplerenone may serve as partial agonists, resulting in some level of co-regulator recruitment at high concentrations. Finerenone is the best studied nsMRA. It was shown to inhibit fibrosis more effectively than steroidal MRAs,[92 93] and it distributes more evenly between the heart and kidneys in experimental animals.[94] However, although its organ protective effects are pronounced, finerenone is a weak antihypertensive.[93]

Mineralocorticoid receptor overactivation promotes inflammation and fibrosis and determines renal disease progression in type 2 diabetes, so treatment with nsMRAs was logical in this population. Phase III RCTs in patients with diabetic kidney disease have shown that finerenone reduces major renal (FIDELIO-DKD) and cardiovascular (FIGARO-DKD) events when added to maximally tolerated renin-angiotensin system inhibition.[92 95 96]

Esaxerenone, which is approved for the treatment of primary hypertension in Japan, was shown to be more effective at controlling blood pressure (5 mg dose) than eplerenone (50 mg) in the ESAX-HTN phase III trial of 1001 Japanese patients.[97] In a placebo controlled trial in patients with diabetes, esaxerenone added to existing renin-angiotensin system inhibitor therapy reduced progression of albuminuria.[98] The urinary albumin-to-creatinine ratio percentage change from baseline to the end of

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treatment was higher with esaxerenone than with placebo (−58% *v* 8%; geometric least squares mean ratio to placebo 0.38, 95% CI 0.33 to 0.44). Significant improvement was seen with esaxerenone compared with placebo in time to first remission (hazard ratio 5.13, 95% CI 3.27 to 8.04) and time to first transition to urinary albumin-to-creatinine ratio ≥300 mg/g creatinine (hazard ratio 0.23, 0.11 to 0.48). Other nsMRAs under investigation include apararenone and ocedurenone.[99-101] In the phase II BLOCK-CKD study of ocedurenone in 162 patients with stage 3B/4 CKD, 89% of whom had resistant hypertension, the low 0.5 mg dose reduced office blood pressure by 10.6 mm Hg (placebo subtracted). These agents may find their greatest benefit in providing more effective treatment of resistant hypertension in patients with diabetic kidney disease.

Aldosterone synthase inhibitors

The role of aldosterone in resistant hypertension and the frequency with which primary aldosteronism causes resistant hypertension led to optimism about the value of ASIs in management of resistant hypertension. Interest in ASIs is augmented by the fact that this class blocks both the genomic and non-genomic effects of aldosterone,[102] in contrast to MRAs. Figure 4 shows the different effects of ASIs compared with MRAs. The *CYP11B2* gene, which encodes aldosterone synthase in the adrenal glomerulosa, shares 93% sequence similarity with *CYP11B1* that encodes for 11β-hydroxylase in the adrenal fasciculata, involved in synthesis of cortisol. Accordingly, a critical element in the development of ASIs has been to avoid inhibiting the synthesis of cortisol. Baxdrostat, lorundrostat, and dexfadrostat are all highly selective inhibitors of aldosterone synthase, with baxdrostat being the best studied. BrigHTN was a phase II multicenter, placebo controlled trial which showed that baxdrostat lowered blood pressure in 248 patients with resistant hypertension.[103] All patients were on stable doses of at least three antihypertensive agents, including a diuretic, and were randomized to receive baxdrostat once daily for 12 weeks or placebo. Systolic blood pressure decreased by 20.3, 17.5, and 12.1 mm Hg with 2 mg, 1 mg, 0.5 mg of baxdrostat, respectively, compared with a fall of 9.4 mm Hg in the placebo group. Of note, only office blood pressures were measured. Potassium concentrations increased to ≥6.0 mmol/L in two patients taking baxdrostat.

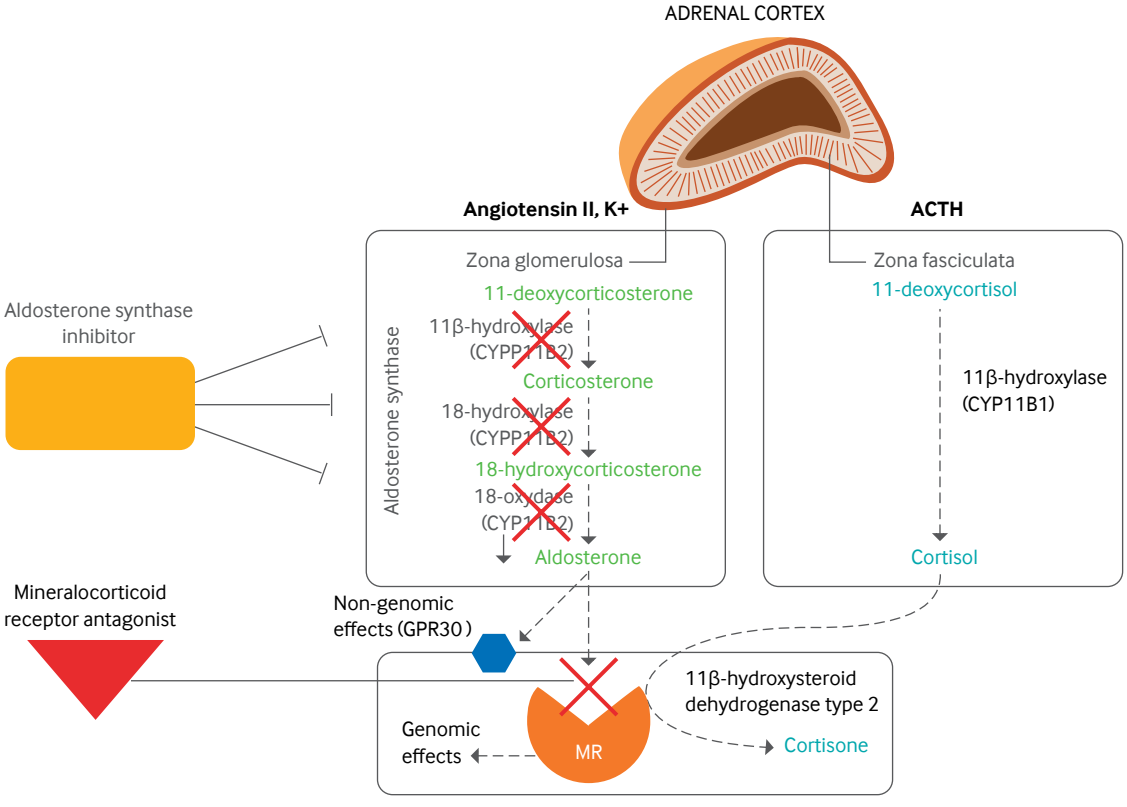

Fig 4 | Inhibition of aldosterone synthase by aldosterone synthase inhibitors (ASIs) reduces production of aldosterone, which results in less stimulation of mineralocorticoid receptors (MRs). How different its effects are from those of MR antagonists (MRAs) remains to be established. ASIs seem to be quite selective for CYP11B2 (aldosterone synthase) present in the zona glomerulosa of the adrenal gland and do not seem to inhibit CYP11B1 present in the zona fasciculata and involved in cortisol synthesis. Cortisol can stimulate the MRs, but is inactivated to cortisone by 11β-hydroxysteroid dehydrogenase type 2 (11βHSD2) associated with MR except in cardiomyocytes, where cortisol can stimulate MRs because of absence of 11βHSD2

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No serious adverse events were reported, and no evidence of hypocortisolemia was seen. Following this positive study, a phase III, multicenter, randomized, double blinded, placebo controlled trial is under way to evaluate once daily 1 mg or 2 mg baxdrostat versus placebo, to reduce systolic blood pressure in ~720 participants with hypertension despite taking two or three antihypertensive agents at baseline (ClinicalTrials.gov NCT06034743).

Other aldosterone synthesis inhibitors may be useful in the future treatment of resistant hypertension. Dexfadrostat phosphate has been shown to suppress the aldosterone/renin ratio, an indicator of sodium retention, in healthy volunteers, also without reduction of cortisol concentrations.[104] Lorundrostat lowered blood pressure effectively in a small RCT in patients with uncontrolled hypertension.[105] Systolic blood pressure fell by 10.1 mm Hg and 13.8 mm Hg with lorundrostat twice daily doses of 12.5 mg and 2 mg, respectively. The mean difference in systolic blood pressure between placebo and treatment was −9.6 (90% CI −15.8 to −3.4) mm Hg) (P=0.01) with a 50 mg once daily dose and −7.8 (−14.1 to −1.5) mm Hg (P=0.04) with 100 mg daily. Six participants had increases in serum potassium above 6.0 mmol/L that required dose reduction or discontinuation of the drug. No reduction in cortisol was reported. Whether reducing aldosterone synthesis could be superior to mineralocorticoid receptor blockade in patients with resistant hypertension, and equivalent to adrenalectomy in patients with aldosterone producing adenoma, remains to be proven.

Angiotensinogen synthesis inhibitors

Pharmacologic blockade of the renin-angiotensin system is available at multiple levels, with suppression of angiotensinogen being the newest promising target. Angiotensinogen is the sole precursor of angiotensin peptides and sits at the first and rate limiting step of the renin-angiotensin system. Lowering angiotensinogen concentrations will reduce the concentration of angiotensins in blood and tissues, and consequently blood pressure. Blood pressure has been shown to be proportional to concentrations of angiotensinogen in the circulation.[106]

Two main approaches to the molecular modification of angiotensinogen are antisense oligonucleotides that inhibit RNA translation and siRNAs. Both result in degradation of target mRNA and reduce hepatic angiotensinogen synthesis.[107] A decrease in liver derived angiotensinogen may result in lowering of blood pressure for several months, which allows for drug administration every three to six months. In a phase I study, 107 patients with hypertension were randomly assigned in a two-to-one ratio to receive either a single ascending subcutaneous dose of zilebesiran (10-800 mg) or placebo and followed for 24 weeks. Circulating angiotensinogen decreased proportionally to the dose of zilebesiran, with 90% suppression after the 800 mg dose, and systolic and diastolic blood pressure decreased for more than 24 weeks in correlation with dose. Dose dependent reductions in serum angiotensinogen following a single injection of zilebesiran were sustained for up to 24 weeks.[107] Most adverse events were mild or moderate in severity, with no hypotension, hyperkalemia, or worsening of renal function. Following these encouraging results, the phase II KARDIA-1 study enrolled 394 patients. Patients were randomized to placebo or four different zilebesiran doses after antihypertensive medication washout. Sustained dose dependent reductions in angiotensinogen were again seen, together with substantial blood pressure lowering in adults with mild-to-moderate hypertension for up to six months.[108] A sustained ~90% suppression of angiotensinogen correlated with durable reduction in blood pressure.

The antisense oligonucleotide targeting angiotensinogen (IONIS-AGT-LRx) has been studied in two small studies.[109] A third study is ongoing (ASTRAAS) with 136 participants with uncontrolled blood pressure taking at least three antihypertensive drugs (NCT04714320).

An antihypertensive delivered by injection with effects enduring to three or six months could represent a significant response to the challenge of apparent resistant hypertension and a major advance in our ability to control blood pressure and improve adherence to treatment.[110] Selective studies in patients with resistant hypertension are needed. Given the dramatic and sustained reduction in angiotensinogen, long term safety data in large numbers of patients will be critical.

Angiotensin receptor blocker associated with a neprilysin inhibitor

The coadministration of the ARB valsartan with the neutral endopeptidase (neprilysin) inhibitor sacubitril was a powerful antihypertensive in preclinical studies and protected the heart from fibrosis in the spontaneously hypertensive rat.[111] The combination was later developed as the heart failure agent Entresto. It has also been approved in some countries for the treatment of difficult-to-control hypertension, and it lowered blood pressure in patients with heart failure and preserved ejection fraction with resistant hypertension who participated in the PARAGON-HF trial.[112] In this RCT, 731 (15.2%) patients had apparent resistant hypertension and 135 (2.8%) had apparent MRA resistant hypertension. Patients with apparent resistant hypertension had a higher rate of primary outcome (17.3 (95% CI 15.6 to 19.1) per 100 person years) than did those with a controlled systolic blood pressure (13.4 (12.7 to 14.3) per 100 person years). The reduction in systolic blood pressure at weeks 4 and 16 was greater with sacubitril-valsartan than with valsartan in the patients with apparent resistant hypertension (−4.8 (−7.0 to −2.5) and 3.9 (−6.6 to −1.3) mm Hg) and apparent MRA resistant hypertension (−8.8 (−14.0 to −3.5) and −6.3 (−12.5 to −0.1) mm Hg). In 47.9%

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of patients with apparent resistant hypertension in the sacubitril-valsartan group and 34.3% of the valsartan group, controlled systolic blood pressure was achieved by week 16 (adjusted odds ratio 1.78, 95% CI 1.30 to 2.43).

Devices for treatment of resistant hypertension

Interest in procedural interventions to manage resistant hypertension is resurging, spurred on by disappointing global rates of blood pressure control despite the longstanding availability of multiple classes of effective drugs. From their beginnings, these devices were tested specifically to treat patients with resistant hypertension. Devices with several modalities of action have been explored, but the intervention supported by the most efficacy and safety data is catheter based renal denervation, an intervention to interrupt sympathetic tone via ablation of the renal nerves.

Renal denervation

After decades of research, two different systems to denervate the kidney by catheter based ablation of the renal nerves were approved by the FDA in 2023 (table 4). The idea emerged from data supporting the importance of renal sympathetic nervous system activation in the pathogenesis of hypertension. Efferent renal nerve stimulation increases blood pressure by increasing sodium reabsorption and renin secretion; afferent outflow is involved in central sympathetic drive contributing to hypertension. Both limbs are targeted with renal denervation. In the 1940s and 1950s, surgical lumbar sympathectomy was done in thousands of patients with resistant hypertension. This surgical procedure lowered blood pressure significantly in about half of patients, but serious side effects including severe orthostatic hypotension often resulted.

Novel technologies using percutaneous sympathetic denervation of the renal arteries began to show benefit before the turn of the millennium.[113 114] In 2009 a small, open label, proof-of-concept study tested radiofrequency renal denervation to treat patients with resistant hypertension. Patients treated with renal nerve radiofrequency ablation with a unipolar electrode catheter showed a remarkable 22/11 mm Hg drop in blood pressure at six months.[115] The randomized Symplicity HTN-2 trial compared renal denervation with standard care and similarly showed a marked difference in blood pressure between groups at six months of 33/11 mm Hg.[116] As a result, renal denervation was added to some society guidelines for the treatment of resistant hypertension. However, the field drew to a dramatic halt with the publication of Symplicity HTN-3, a prospective single blind trial that included a sham procedure arm but showed no significant difference in blood pressure lowering between groups.[117] A moratorium was effectively placed on the procedure, and the research field underwent a reset.

Changes in study design and methods have been guided by a set of position papers on clinical trial design and conduct.[118-125] A second wave of randomized, sham controlled, blinded studies of renal denervation followed, which cumulatively have shown safety and efficacy in controlling hypertension.

The radiofrequency program continued with the advanced Spyral multielectrode catheter treating the main renal artery as well as branches and accessories. The multicenter SPYRAL HTN-OFF MED randomized pivotal trial enrolled 331 patients off antihypertensive medication and showed 3.9 (bayesian 95% CI −6.2 to −1.6) mm Hg greater 24 hour reduction in systolic blood pressure with renal denervation compared with sham at three months.[126] In the SPYRAL HTN-ON MED Extension trial, 337 patients with moderate to severe hypertension taking one to three antihypertensive drugs were randomized, and no significant difference was seen in 24 hour ABPM reduction with renal denervation compared with the sham group (−6.5 *v* −4.5 mm Hg). However, a greater increase in medication use was seen in the sham group with greater falls in office blood pressure.[127]

An alternative technology, ultrasound based renal denervation, has been used with the PARADISE system, which achieves a circumferential ring of ablation outside the vessel lumen and which centers the transducer inside a water filled protective cooling balloon. Unlike with radiofrequency, the distal branches do not need to be treated with the PARADISE system. All three of the multicenter, randomized, sham controlled trials met their primary endpoint: a greater fall in daytime ambulatory systolic blood pressure at two months compared with sham. These included patients with mild hypertension treated in the absence of all medicines in RADIANCE-HTN SOLO (146 patients randomized),[128] with a reduction in daytime ambulatory systolic blood pressure greater with renal denervation (−8.5 (SD 9.3) mm

Table 4 | Devices

Technology	Device name	Status
Radiofrequency RDN	SPYRAL	FDA approval Nov 2023
Ultrasound based RDN	PARADISE	FDA approval Nov 2023
Alcohol ablation RDN	Peregrine	Pivotal trial published April 2024
Cardiac neuromodulation	BackBeat CNT	Global pivotal trial under way
Carotid baroreceptor modulation	MobiusHD	Program cancelled; no longer recommended in guidelines

FDA=Food and Drug Administration; RDN=renal denervation.

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Hg) than with the sham procedure (−2.2 (10.0) mm Hg; baseline adjusted difference between groups −6.3 (95% CI -9.4 to -3.1) mm Hg; P=0.001). RADIANCE-HTN II (150 patients), an independently powered study of patients with mild-to-moderate hypertension treated off medications, also showed reduction in daytime ambulatory systolic blood pressure to be greater with ultrasound based renal denervation (mean −7.9 (SD 11.6) mm Hg) than with sham procedure (−1.8 (9.5) mm Hg; baseline adjusted between group difference −6.3 (95% CI −9.3 to −3.2) mm Hg; P<0.001).[129] Finally, patients with true resistant hypertension were studied in RADIANCE-HTN TRIO (136 patients),[130] which showed that renal denervation reduced daytime ambulatory systolic blood pressure more than the sham procedure (−8.0 *v* -3.0 mm Hg; median between group difference −4.5 (95% CI −8.5 to −0.3) mm Hg; adjusted P=0.022). The median between group difference was −5.8 (-9.7 to −1.6) mm Hg (adjusted P=0.005) among participants with complete ambulatory blood pressure data. In a pooled analysis of more than 500 patients treated in these three RADIANCE ultrasound trials, daytime ambulatory systolic blood pressure fell by 8.5 mm Hg versus 2.9 mm Hg for sham, with a mean difference of 5.9 mm Hg (P<0.001) in favor of ultrasound based renal denervation.[131]

Head-to-head comparison of the two devices in small groups of patients found that blood pressure was reduced to a greater degree in the ultrasound based renal denervation group than with radiofrequency of the main renal artery only (−13.2 (standard deviation 13.7) versus −6.5 (10.3) mm Hg), but not statistically greater than radiofrequency of the main and side branch ablation (mean difference −4.9 mm Hg).[132] The difference may be caused by deeper penetration of energy and more complete sympathetic nerve ablation with ultrasound based renal denervation. These results need to be replicated in a larger cohort with longer follow-up.

Both devices have shown a remarkable safety profile over three years in controlled trials, and longer in observed cohorts.[133-135] The FDA expert Circulatory System Devices Panel voted unanimously in favor of safety. Theoretical concerns about renal artery stenosis existed, but the incidence has been extremely low, with no major procedure related safety events. Similarly, no evidence that renal denervation causes progression of decline in GFR has been found, with some evidence suggesting that it may offer renal protection.[136] Durability of effect has been shown over three years in clinical trials.[137 138] Promising longer term results have emerged from the Global Symplicity Registry 10 year follow-up study.[139]

Unresolved questions remain. The main one is identification and predictors of who will respond, as about two thirds of patients respond to the procedures with a fall in systolic blood pressure greater than 5 mm Hg compared with sham. The only universal predictor of a larger blood pressure response to date has been higher baseline blood pressure, although hemodynamic variables such as heart rate and orthostatic hypertension, both considered indicators of sympathetic activity, were associated in some analyses.[131 140] Arterial stiffness has also been associated with the blood pressure response.[141 142] Evidence for the predictive value of an overactive renin-angiotensin system on blood pressure response has been mixed.[143 144]

A third catheter renal denervation system uses dehydrated alcohol as a neurolytic agent.[145] In the TARGET BP-OFF-MED study of 106 patients not taking or withdrawn from antihypertensive drugs, no significant difference was seen between treatment and sham groups (2.9 *v* 1.4 mm Hg).[146] The pivotal TARGET BP I blinded sham procedure trial evaluated the Peregrine system in 301 patients with uncontrolled hypertension despite being treated with two to five antihypertensive drugs. It met its primary endpoint for efficacy, with a significant although modest reduction in 24 hour ambulatory systolic blood pressure at three months compared with sham (mean -10.0 (SD 14.2) *v* -6.8 (12.1) mm Hg; treatment difference −3.2 (95% CI −6.3 to 0.0) mm Hg; P=0.048).[147]

European, Asian, and American expert consensus statements are in general agreement in support of renal denervation as a potential adjunct treatment in patients with uncontrolled hypertension despite best efforts at lifestyle and medication interventions.[123 124 148] These statements offer advice about patient selection, as renal denervation is not appropriate for everyone with hypertension. The most obvious patients for whom this procedure should be considered are those with true resistant hypertension. But expert recommendations are broader, as is the FDA indication: to reduce blood pressure as an adjunctive treatment in patients with hypertension in whom lifestyle modifications and antihypertensive medications do not adequately control blood pressure. Many patients have uncontrolled hypertension because they cannot manage to take sufficient drug therapy for a host of reasons. This provides a reason to discuss renal denervation with some patients who do not have true resistant hypertension. Several studies have shown that many patients would prefer renal denervation to taking additional medicine for their high blood pressure.[149-152] Shared decision making is a necessary component of patient evaluation for this procedure.

Carotid baroreceptor modulation

A device based method targeting carotid baroreflex activation was first tested with implantable electric stimulators (Rheos System), which lowered blood pressure effectively in patients with resistant hypertension.[153-155] The MobiusHD endovascular baroreceptor amplification device was a less invasive therapy. Mobius was first tested in 30 patients with resistant hypertension in the CALM-FIM EUR open label study, in which blood pressure reduction was dramatic; a three year follow-up in 47 patients

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showed a sustained fall in blood pressure,[156] but serious adverse events raised concern. The CALM-2 study was cancelled and no study of endovascular baroreceptor amplification in hypertension is ongoing. ESH/ESC guidelines no longer recommend baroreflex stimulation.[67]

Cardiac neuromodulation therapy

Cardiac neuromodulation therapy involves programming a sequence of variably timed short and longer atrioventricular intervals to reduce blood pressure; hence, it is also known as atrioventricular interval modulation therapy. This treatment is compatible with standard pacemakers. A double blind pilot study (Moderato II, BackBeat Medical) randomized 47 patients with uncontrolled hypertension despite taking at least one antihypertensive drug who already had an indication for a dual chamber pacemaker. After six months, ambulatory systolic blood pressure was reduced by 8.1 mm Hg compared with the control group, with no device related adverse events.[157] BackBeat cardiac neuromodulation therapy will be tested in a global pivotal trial randomizing about 500 patients who have an indication for, and have recently received, a cardiac pacemaker implant. The target population for this treatment is the majority of ~1.1 million people globally who are implanted with cardiac pacemakers each year who also have hypertension.

Emerging drug treatments

Atrial natriuretic peptides were discovered more than 40 years ago but have not found a clinical indication to date, apart from diagnostic value in heart failure. M-atrial natriuretic peptide represents the first of its class to be developed for the treatment of hypertension. To date, only one small open label, single dose trial has been reported, which showed lowering of blood pressure accompanied by a dose dependent increase in urinary sodium excretion.[158] Another new target for antihypertensive therapy is aminopeptidase A, which converts angiotensin II to the pressor angiotensin III. Preclinical testing identified an inhibitory molecule, EC33,[159] which reduced systemic vasopressin, decreased sympathetic tone, and stimulated the baroreflex.[160] Firibastat is a prodrug that is metabolized to release EC33. It lowered blood pressure in an eight week, multicenter, open label, phase IIb study of 256 patients with stage 2 primary hypertension.[161] The phase III double blind FRESH trial failed to show a decrease in unattended automated office systolic blood pressure in a population of patients with difficult-to-treat and resistant hypertension.[162]

A developing plan is to combine antihypertensive drugs that retain volume with sodium-glucose cotransporter type 2 inhibitors, to combat sodium retention and enhance blood pressure lowering effects. Whether this approach will become effective in improving the treatment of resistant hypertension, particularly in the presence of impairment of renal function, remains to be demonstrated.

Guidelines

The AHA's 2017 hypertension guidance was followed by a statement dedicated to the detection, evaluation, and management of resistant hypertension in 2018.[14] The ESH guidelines were renewed in 2023.[67] Both agencies agree on several important factors, emphasizing the importance of discriminating between apparent and true resistant hypertension by confirming hypertensive out-of-office blood pressure and excluding non-adherence to antihypertensive medication. The definitions of true resistant hypertension are similar, with both guidelines including uncontrolled blood pressure despite taking an ACE inhibitor or ARB, a CCB, and a diuretic at maximum or maximally tolerated doses. The diagnostic threshold is ≥130/80 mm Hg in the US, whereas the ESH incorporates an office blood pressure of 140/90 mm Hg, confirmed by out-of-office blood pressure measurement showing uncontrolled 24 hour blood pressure ≥130 or ≥80 mm Hg. Both focus on optimizing lifestyle changes and medical therapy, including combination therapies. US guidelines advise spironolactone as fourth line, whereas the ESH guidelines recommend that the fourth drug should be chosen on the basis of eGFR: spironolactone in patients with eGFR >30 mL/min and chlorthalidone in those with eGFR <30 mL/min. In a novel step, the 2023 ESH hypertension guidelines include renal denervation as an additional treatment to be considered in patients with resistant hypertension (class of recommendation II).[67] A 2020 consensus document from Asia and a 2023 resistant hypertension consensus document from the Korean Society of Hypertension support most of the approaches that have been summarized here.[148 163]

Conclusion

Resistant hypertension remains a highly prevalent, impactful clinical dilemma. The percentage of hypertensive patients with resistant

GLOSSARY OF ABBREVIATIONS

- ABPM—ambulatory blood pressure monitoring
- ACE—angiotensin converting enzyme
- AHA—American Heart Association
- AOBP—Automated office blood pressure measurement
- ARB—angiotensin receptor blocker
- ASI—aldosterone synthase inhibitor
- CCB—calcium channel blocker
- CKD—chronic kidney disease
- eGFR—estimated glomerular filtration rate
- ESC—European Society of Cardiology
- ESH—European Society of Hypertension
- FDA—Food and Drug Administration
- MRA—mineralocorticoid receptor antagonist
- nsMRA—non-steroidal mineralocorticoid receptor antagonist
- RCT—randomized controlled trial
- siRNA—small interfering RNA

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QUESTIONS FOR FUTURE RESEARCH

- As non-adherence to antihypertensive drugs underlies much of resistant hypertension, how can we best assess adherence and how best maximize it?
- Will the availability of a durable treatment taken monthly or even yearly, instead of daily pills, be game changing for treatment of resistant hypertension, as it has been for diabetes, hyperlipidemia, and osteoporosis?
- With the high prevalence of primary aldosteronism responsible for much of resistant hypertension, would the routine targeted use of mineralocorticoid receptor antagonists or eventually aldosterone synthase inhibitors be the most effective approach to this condition globally?
- What will be the cost effectiveness of novel agents and devices in the treatment of apparent or true resistant hypertension, assessed by large scale examinations of their long term efficacy and safety?

hypertension and exposed to the associated serious complications, morbidity, and mortality is very large.[164] Recent large randomized multicenter trials have shown the efficacy of adding MRAs or endothelin antagonists and of different devices to control blood pressure in resistant hypertension.[165] Some guidelines for management of hypertension have already incorporated these findings to some degree, and good practice should include them in the management of hypertensive patients in clinical practice.

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